BOARD-INVITED REVIEW: The biology and regulation of preadipocytes and adipocytes in meat animals

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J Anim Sci 2009.87:1218-1246.
doi: 10.2527/jas.2008-1427 originally published online Oct 10, 2008;

BOARD-INVITED REVIEW: The biology and regulation of preadipocytes and adipocytes in meat animals[1,2]

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ABSTRACT: The quality and value of the carcass in domestic meat animals are reflected in its protein and fat content. Preadipocytes and adipocytes are important in establishing the overall fatness of a carcass, as well as being the main contributors to the marbling component needed for consumer preference of meat products. Although some fat accumulation is essential, any excess fat that is deposited into adipose depots other than the marbling fraction is energetically unfavorable and reduces efficiency of production. Hence, this review is focused on current knowledge about the biology and regulation of the important cells of adipose tissue: preadipocytes and adipocytes.

Key words: adipocyte, meat animal, preadipocyte, review

J. Anim. Sci. 2009. 87:1218–1246
doi:10.2527/jas.2008-1427

INTRODUCTION

Feeding grain and increasing time on feed improve the palatability and acceptability of meat for the US consumer, primarily by increasing the amount of marbling (e.g., Crouse et al., 1984). To circumvent the obvious waste of resources and resultant inefficiency in production incurred by the overfattening of livestock, it has been the goal of animal scientists to understand the regulation of adipose tissue differentiation. Marbling adipose tissue, also known as interfascicular or intramuscular adipose tissue, represents a unique depot. It can be distinguished from other fat depots by its location within perimysial connective tissues alongside myofibers (Moody and Cassens, 1968), as well as its unique pattern of metabolism. Marbling adipocytes typically display rates of fatty acid biosynthesis that are 5 to 10% of the rates observed in subcutaneous adipose tissue (Hood and Allen, 1978; Smith and Crouse, 1984). Intramuscular adipose tissue incorporates palmitic acid into storage lipids (triacylglycerols) at rates that exceed those in subcutaneous adipose tissue (Lin et al., 1992). The process of triacylglycerol biosynthesis is more sensitive to starvation in subcutaneous than in intramuscular adipose tissue (Smith et al., 1998a). Moreover, glucose contributes a greater proportion of carbon to fatty acid biosynthesis in intramuscular than in subcutaneous adipose tissue (Smith and Crouse, 1984). These data consistently indicate that intramuscular and subcutaneous adipose tissues are metabolically distinct. This difference between adipose tissue depots are likely manifested at the cell level (preadipocytes and adipocytes). Therefore, it is critical and timely to review adipocyte and preadipocyte biology and regulation in food production animals. This review primarily focuses on domestic meat animals and builds

[1]Project originated from the USDA-sponsored regional research project: "Regulation of adipose tissue accretion in meat-producing animals (NCR97)."
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Received August 22, 2008.
Accepted October 2, 2008.

upon several recent reviews (Houseknecht et al., 1998; Hausman et al., 2001; Azain, 2004; Kokta et al., 2004; Novakofski, 2004; Sillence, 2004; Fernyhough et al., 2005, 2007; Jacobi et al., 2006; Rothschild et al., 2007), and research reports: *Biology of Fat in Meat Animals*, published first in 1976 (Allen et al., 1976) and updated in 1995 (Rule et al., 1995; Smith, 1995).

Cells of Adipose Tissue

Adipose tissue is a connective tissue of mesenchyme origin (Scanes, 2003) originating from parental cells similar to those that give rise to muscle cells, chondrocytes, or fibroblasts (Holtzer et al., 1975; Hausman et al., 1980; Gesta et al., 2007). Adipose tissue characteristically possesses substantial blood vessels and associated nerves (Hausman et al., 1980; Crandall and DiGirolamo, 1990; Crandall et al., 1997; Hausman and Richardson, 2004), and the overall mass of adipose tissue increases with age in meat animals but not in all birds (Cartwright, 1991; Owens et al., 1993; Hill et al., 2003; Scanes, 2003).

The cells of adipose tissue appear to be dynamic; a renewed search for the origin of adipocyte progenitors has demonstrated high incidences of cellular plasticity, even in adult adipose tissue (Fernyhough et al., 2005, 2008; Schaffler and Buchler, 2007). Moreover, under certain conditions, adipocyte progenitors may be recruited from the progenitor cell pools in the bone marrow (Gimble et al., 2006; Zeng et al., 2006) with the subsequent incorporation of bone marrow-derived adipocyte progenitor cells into adipose tissue (Crossno et al., 2006).

Although once thought of as simply providing insulation or being a good "padding" material, adipose tissue is quite dynamic and reactive—exerting an influence on the metabolism and functions of other body systems (Jacobi et al., 2006). Adipose tissue secretes or expresses many endocrine factors including leptin, a hormone that influences growth, metabolism, and behavior (Houseknecht et al., 1998; Barb et al., 2001; Spicer, 2001; Kokta et al., 2004; Macajova et al., 2004; Miner, 2004; Sillence, 2004; Trayhurn, 2005; Hausman and Hausman, 2006; Jacobi et al., 2006; Hausman et al., 2007; Wang et al., 2008a). The discovery that adipose tissue is a major source of circulating regulatory compounds launched an era of intensive and multifaceted research, which continues to provide remarkable perspectives on adipocyte and preadipocyte biology and regulation.

Although mature adipose tissue contains various cell types, adipocytes predominate and are the primary storage site for excess energy in the form of triacylglycerols (Azain, 2004). Excess energy is stored in adipocytes to be used during times of negative energy balance (Nafikov and Beitz, 2007), including when feeding is restricted (Flier, 1995). Energy flow into and out of adipocytes is mediated by extrinsic regulators (Lee et al., 1994; Azain, 2004; Kokta et al., 2004; Louveau and Gondret, 2004; Mimbs et al., 2005). Because subcutaneous, internal, seam, and intramuscular adipose tissue depots are all economically and physiologically important in meat animal production, deciphering the regulation of each adipose depot may lead to new strategies of animal production. However, it appears that not all adipose depots within or between animals are similarly maintained or regulated (Hood and Allen, 1973; Allen, 1976; Hood, 1982; Cianzio et al., 1985; May et al., 1995; Sillence et al., 2002; Albrecht et al., 2006; Fernyhough et al., 2007). This not only highlights the difficulties encountered in the thorough study of adipocytes, but also suggests that not all adipocytes are similar in form and function. Furthermore, cellular and functional adipose depot-dependent traits are likely dictated by a combination of intrinsic (genetic) and extrinsic factors (Tchkonia et al., 2006, 2007).

Adipogenesis

Adipogenesis is an inclusive term describing the proliferation, differentiation, and conversion of cells into lipid-assimilating cells found within fat tissue (Hausman et al., 2001; Kokta et al., 2004; Novakofski, 2004; Fernyhough et al., 2007). Adipogenesis is of importance to animal production due to the obvious ramifications of cost-effectively producing healthy animals that yield products with high consumer appeal (Mir et al., 2002, 2008; Bergen and Mersmann, 2005; Dhiman et al., 2005; Givens, 2005).

From an Embryonic Mesodermal Cell to the Adipocyte. The embryonic development of mesodermal cells to form committed preadipocytes/adipofibroblasts has been described (Otto and Lane, 2005). Cells within budding embryonic and fetal adipose tissue depots undergo adipogenesis in an asynchronous manner (Hausman and Richardson, 2004), and postnatal adipocytes form more rapidly (as a function of available energy and regulation; Azain, 2004). Strategies to alter initial formation of adipose depots through the manipulation of embryonic mesodermal cells or initially formed preadipocytes/adipofibroblasts have been suggested (McMillen et al., 2004; Mir et al., 2008).

To Proliferate or Differentiate? Traditionally, cells undergoing adipogenesis are thought of as being terminally differentiated when they express numerous cellular or molecular markers reflective of lipid assimilation into storage triacylglycerol. There is some evidence, at least in cell culture, that suggests that mature adipocytes containing considerable lipid may still proliferate (Figure 1, Fernyhough et al., 2005, 2007).These observations imply that the cellularity of an adipose depot may be a function of 3 different cell populations (Dodson and Fernyhough, 2008; Fernyhough et al., 2008). First, nondifferentiated stem cell cells may experience a transdifferentiation event to become preadipocytes, which possess the ability to accumulate lipid. Second, proliferative-competent preadipocytes from embryonic development that are found in adipose depots may add

conversion-competent cells to the enlarging adipose tissue depot. Finally, mature cells may reinitiate proliferation and add new cells to the growing adipose tissue.

What Drives Adipogenesis? The fate of adipocyte precursor cells depends on the convergence of multiple factors including adhesion of cells to the surrounding extracellular matrix (**ECM**) or to neighboring heterologous and homologous cells, the mix of growth factors and endocrine environment, neural inputs, and the availability of macro- and micro-nutrients. The metabolic and morphological characteristics acquired during adipocyte differentiation reflect increased downstream transcript activity from targets of the adipogenic transcription factors peroxisome proliferator activated receptor (**PPAR**) and CCAAT-enhancer binding protein (**C/EBP**). Expression of other DNA binding proteins (**Id**), which form heterodimers with helix-loop-helix transcription factors, are modu-

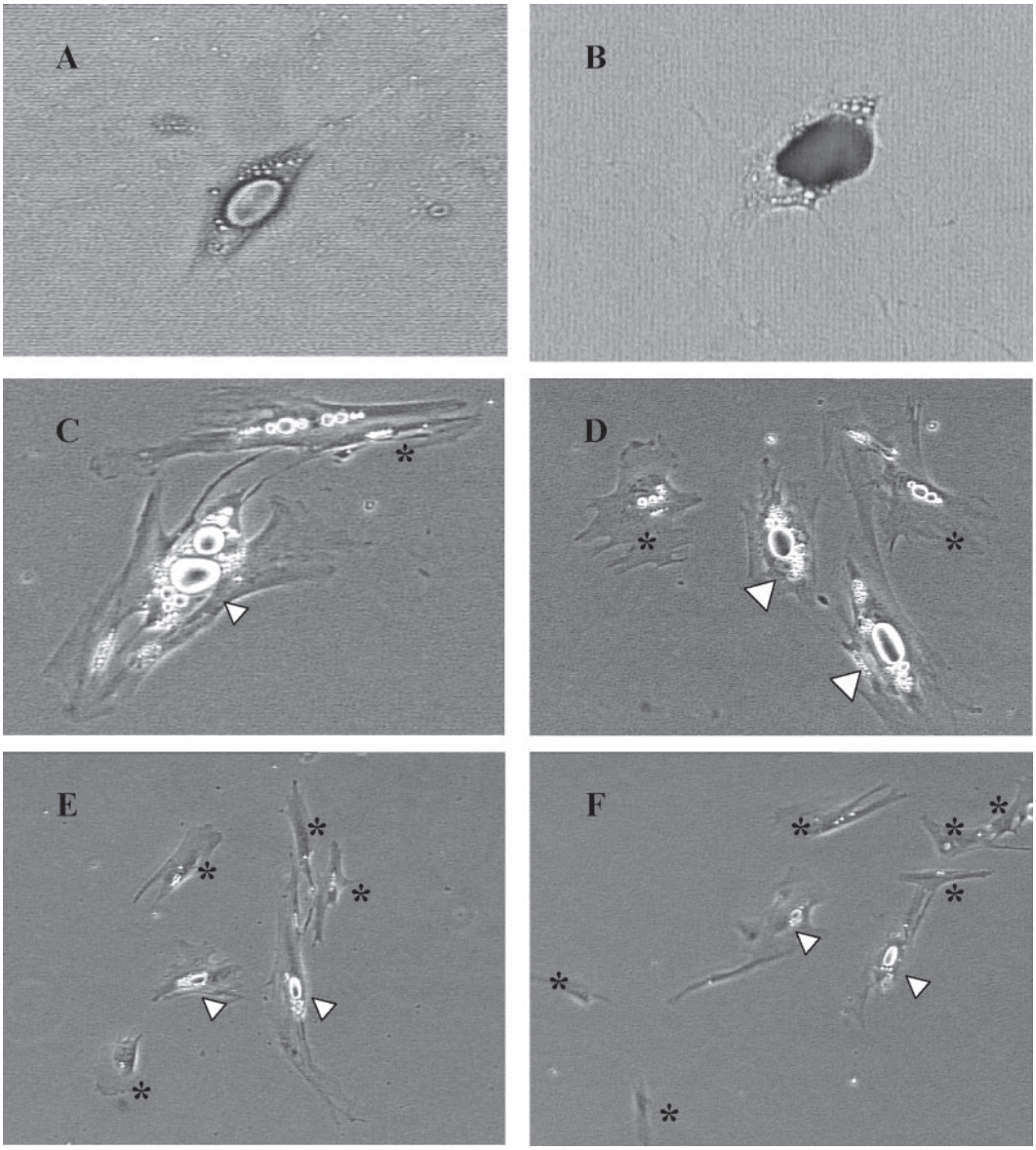

Figure 1. Mature beef-derived adipocytes display the ability to revert to proliferative-competent cells in vitro. Panel A: phase contrast photomicrograph of mature adipocyte in vitro (20×). Panel B: same cell as in panel A, but after fixing and staining for Oil-Red-O uptake by lipid and using bright field microscopy (20×). The cell in panel B could not be propagated any longer due to the cell dying during the fixing/staining procedure. Panel C: 2 lipid-containing mature beef-derived adipocytes undergoing proliferation after a total of 8 d in culture and 24 h on a basal medium of Dulbecco's modified Eagle medium (DMEM) + 10% FBS (40× magnification). Arrowhead and * mark the cells to allow following the cell through subsequent divisions. Panel D: after 48 h of exposure to DMEM + 10% FBS, the 2 mature cells had divided to produce 2 more daughter cells (*, arrowheads), possessing half the complement of lipid of the parental cell (20× magnification). Panels E-F: photomicrographs of a colony of proliferative adipofibroblast cells derived from the dedifferentiation of mature adipocytes in panel C. Each subsequent division of cells resulted in a decreased amount of detectable lipid in each daughter cell (*, arrowheads). Panels C-D: photomicrographs were taken with a Nikon inverted Diaphot microscope, equipped with Sony RGB (0.6 in chip) camera and Optix image analysis system (Meridian Instruments, Olympia, WA), and originally appeared in Fernyhough et al. (2005; used with permission). Daughter cells such as these may be expanded for use in comparative studies with other types of preadipocytes or stromal vascular cells, as well as to determine if they possess stem cell-like characteristics (Fernyhough et al., 2008).

lated by histone methylation and preserve the stem cell state and prevent lineage determination (Iavarone and Lasorella, 2006). The Id proteins interact with cyclin-dependent kinase inhibitors to maintain proliferation and with sterol regulatory element binding protein-1c (**SREBP-1c**) to suppress PPARγ and its downstream targets to inhibit differentiation (Moldes et al., 1999). Lineage specification of precursor cells is strongly modulated by both a cell and the ECM. The ECM adhesion molecules as well as adhesion signaling components change with adipose differentiation (Liu et al., 2005; Li and Xie, 2007). Adhesion likely remains important in differentiated adipose function in a variety of cell types (Murad et al., 2007). Also, the inflammatory changes of adipose tissue associated with obesity involve changes in adhesion molecules and adhesion-related matrix proteases (Gil et al., 2007). The contemporary view of cells comprising adipose tissue is surprisingly complex and includes multipotent mesenchymal stem cells, multipotent vascular progenitor cells, unipotent preadipocytes, and endothelial progenitor cells. It is also apparent these additional cell types may be depot-specific (Tchkonia et al., 2007).

Quantitative Assessment of Adipogenesis. Complex empirical computer models have proven useful in predicting the effects of genotype and nutrition on growth and body composition in beef cattle, swine, and other species, as well as factors capable of simulating adipocyte development and metabolic fluxes of differentiated adipocytes in a variety of species including rats, mice, sheep, pigs, humans, and cattle (Bywater et al., 1988; Di Marco and Baldwin, 1989; Sainz and Wolff, 1990). The DiMarco and Baldwin (1989) and Sainz and Wolff (1990) computer models represent lipogenesis and lipolysis in adipose explicitly, but adipocyte hyperplasia is not represented (Di Marco and Baldwin, 1989; Sainz and Wolff, 1990). Similarly, the computer model by Hoch and Agabriel (2004) represents lipid accretion in cattle as a function of the rates of lipogenesis and lipolysis, with no regard for changes in cellularity.

Presently, there are intermediate computer models that incorporate mechanistic elements into empirical frameworks to improve their applicability over a wider range of intrinsic and extrinsic conditions. In the Davis growth model, a single DNA pool represents the number of cells (nuclei) in the body, and this in turn determines the rate of protein synthesis. The Davis growth model has been tested extensively (Barioni et al., 2006; Garcia et al., 2007; McPhee et al., 2007a,b), is capable of simulating cattle growth and body composition under a wide range of conditions, and may be subsequently extended by adding explicit representations of hyperplasia and hypertrophy of adipocytes in 4 depots: visceral, intermuscular, subcutaneous, and intramuscular. However, additional research is needed to improve our quantitative understanding of the intrinsic and extrinsic factors that determine adipocyte hyperplasia and hypertrophy in different adipose depots.

Extrinsic Regulation

Adipocyte differentiation is under the regulation of multiple hormones and growth factors. These initiate intracellular signal transduction through cell surface or intracellular receptors expressed on preadipocytes. The requirement for hormones for the differentiation program of the adipocyte is underscored by the need for serum in the differentiation media and in standard adipogenic cocktails used in many in vitro models of adipogenesis. A cocktail of serum, which supplies multiple hormones and growth factors, insulin, glucocorticoids (often dexamethasone), and isobutylmethylxanthine is sufficient for the differentiation of 3T3-L1 cells (Fernyhough et al., 2007). Hormonal stimulation of preadipocytes leads to an increase in the level of intracellular cyclic adenosine monophosphate (**cAMP**), which is considered a prerequisite for initiating differentiation. In 3T3-L1 preadipocytes the differentiation cascade is marked by a sequential expression of the α, β, and δ isoform of C/EBP (Fujimoto et al., 2005). The expression of C/EBP β and δ expression occurs within 24 to 48 h following addition of the differentiation cocktail to 3T3-L1 cells (Fujimoto et al., 2005). The initial appearance of C/EBP β and δ appears to be necessary for the appearance of 2 downstream transcription factors, C/EBPα and PPARγ, which are involved in the late stages of the differentiation program (Farmer, 2005; Rosen, 2005). The appearance of PPARγ and C/EBPα ensures the maintenance of the differentiated state of the adipocytes, and the 2 transcription factors reciprocally regulate each other (Rosen, 2005). Although C/EBP β and δ are responsible for the induction of PPARγ, SREPB proteins are also involved regulation PPARγ expression (Otto and Lane, 2005). However, there is apparent species variation in the temporal pattern of appearance of these transcription factors. In rat, pig, and human stromal vascular (**SV**) cell culture, the presence of both the mRNA and protein of PPARγ and C/EBPα, β, and δ has been confirmed very early after isolation (Tchkonia et al., 2002; Tomlinson et al., 2006). Additionally, bovine SV cells also express PPARγ and C/EBPβ mRNA despite the absence of adipogenic induction (Hirai et al., 2007a,b). In contrast to 3T3-L1 cells, cultures of SV cells and fetal tissue indicate a lack of temporal demarcation of expression of CEBP α, β, and δ such that these are concurrently or stably expressed in both the undifferentiated and the full differentiated states (Tomlinson et al., 2006; Hirai et al., 2007a,b). It is possible that an in vivo environment, replete with hormones and other endogenous adipogenic factors, may have preprogrammed SV cells to express these transcription factors early in culture and with a pattern that differs from that observed in 3T3-L1 cells (Fernyhough et al., 2007).

Insulin/IGF-1. Adipocyte differentiation may be induced by both IGF-1 and insulin. However, because preadipocytes express very few insulin receptors, adi-

pogenic response to insulin is thought to be due to the transactivation of the IGF-1 receptor by insulin at the supraphysiological concentrations (Holly et al., 2006; Fernyhough et al., 2007). Responsiveness to insulin and the abundance of insulin receptors increases dramatically as the cells undergo terminal differentiation to adipocytes (Shimizu et al., 1986). Primary SV cells express the IGF-1 receptor (Chen et al., 1995), which increases preadipocyte replication (Wright and Hausman, 1995) and differentiation in some adipogenic cell lines (Boney et al., 1994) and primary SV cell cultures (Richardson et al., 1998). The IGFBP can modulate the function of IGF-1 on adipocyte differentiation. In pig and rabbit SV cultures, expression of IGFBP is regulated by adipogenic and antiadipogenic hormones (Chen et al., 1996), and accumulation of IGFBP-1 in developing porcine adipose tissue correlates with a significant suppression of cell proliferation. The IGF-1 stimulates both proliferation and differentiation in the 3T3-L1 cells (Boney et al., 2000). Available evidence also indicates that IGF-1 may effectively regulate preadipocyte development in pigs and humans. However, serum insulin concentrations in the pig are less than are IGF-1 concentrations (Sillence and Etherton, 1987), and porcine and human preadipocytes in primary culture also express and secrete IGF-1 and IGFBP (Wabitsch et al., 2000; Hausman et al., 2002).

GH. Also known as ST, GH is a major regulator of IGF-1 expression in preadipocytes (Wabitsch et al., 1996). However, its effect on adipocyte differentiation is dependent on cell type. Whereas GH stimulates adipogenesis in 3T3-F442A preadipocytes by priming the cells for the proliferative effect of IGF-1 (Guller et al., 1991), addition of GH to primary rat preadipocytes in serum-free conditions indicates that GH reduces the formation of new fat cells and the expression of mature adipocyte markers, despite its stimulation of IGF-1 expression and proliferation of cells. Therefore, the induction of IGF-1 by GH may not be sufficient for it to stimulate adipogenesis. Differences in the ECM environment of primary preadipocytes and clonal cell lines may partly be responsible for differences in response to GH. The overall effect of GH on adipocyte differentiation, or differentiation of any other cell in muscle (Allen et al., 1986; Dodson et al., 1987; Molnar and Dodson, 1993), may be a proliferative effect, which is mediated by IGF-1 (Wabitsch et al., 1995). However, GH is a strong lipolytic hormone, which may cause a net reduction in adipose mass even though it enhances IGF-1 action (Duquette et al., 1984; Hart et al., 1984).

Glucocorticoids. Dexamethasone is a synthetic glucocorticoid, which induces the differentiation of primary preadipocytes from multiple species [(humans, pigs, rabbits, rats, and mice); Reyne et al., 1989; Hauner et al., 1989; Gregoire et al., 1991; Litthauer and Serrero, 1992; Suryawan et al., 1997] and aneuploid preadipocyte cell lines (Gaillard et al., 1991). Multiple mechanisms are responsible for the stimulatory effect of glucocorticoid on adipogenesis. First, glucocorticoids such as dexamethasone downregulate the expression of preadipocyte factor-one (**Pref-1**; Smas et al., 1999), a plasma membrane protein that inhibits differentiation (Sul et al., 2000). Deiuliis et al. (2006) also described the identification of the Pref-1 gene in the pig. In agreement with data from 3T3-L1 preadipocytes, Pref-1 is highly expressed in the SV fraction of digested pig adipose tissue relative to mature adipocytes and in adipose tissue from fetal pig tissues relative to adipose tissue from mature pigs (Deiuliis et al., 2006). This suggests that Pref-1 may also be a negative regulator of adipocyte differentiation and adipose tissue development in the pig as well. Because an increase in intracellular cAMP precedes adipocyte differentiation, glucocorticoids are thought to stimulate adipocyte differentiation by stimulating increased conversion of arachidonic acid to prostacyclin, which leads to increased cellular cAMP content (Ailhaud et al., 1992). Additionally, glucocorticoids enhance adipocyte differentiation by stimulating the expression of C/EBP-δ which may promote the dimerization of C/EBP-δ-C/EBP-β and expression of PPARγ (Wu et al., 1996).

Thyroid Hormone. Considerable evidence is available to suggest that thyroid hormone (**T-3**) plays only minimal role in adipogenesis (Ramsay, 1985; Deslex et al., 1987; Hausman, 1989). As suggested by Hausman (1989) stimulation of adipocyte differentiation by T-3 in serum containing media could be dependent on other hormones or growth factors. For example, IGF-1 is elevated in pig serum, whereas insulin concentrations are decreased (Martin et al., 1984; Sillence and Etherton, 1987), which could cause interactions between T-3 and IGF-1 to promote adipocyte differentiation in pigs (Ramsay, 1985).

Other Hormones and Growth Factors. Growth factors such as epidermal growth factor and transforming growth factor (**TGF**) inhibit adipose tissue development. The TGF family inhibits differentiation of 3T3-F442A cells and rat preadipocytes (Luetteke et al., 1993; Serrero and Lepak, 1996). Epidermal growth factor also suppresses adipogenic conversion of mouse, rat, and human preadipocytes (Vassaux et al., 1994; Hauner et al., 1995; Serrero and Lepak, 1996), whereas TGFβ is a potent inhibitor of adipocyte differentiation (Sparks et al., 1992). A possible mechanism for TGFβ inhibition of adipocyte differentiation may be its stimulation of increased ECM component synthesis (Heino and Massague, 1990). However, whether TGFβ directly suppresses adipocyte differentiation may be dependent on the temporal expression of TGFβ during adipogenesis. Others have shown that TGFβ blocks early but not late differentiation-specific gene expression and morphologic differentiation of 3T3-L1 cells (Sparks et al., 1992). Tumor necrosis factor α causes adipocyte insulin resistance and suppresses mature adipocyte phenotype via multiple mechanisms, including suppression of PPARγ or C/EBP-β (Kita et al., 2005), through JNK activation (Kim et al., 2005), or a combination of these. Alone, tumor necrosis factor α causes adipocyte

lipolysis (Ryden et al., 2004) and dedifferentiation that involves stimulation of preadipocyte genes (Ruan et al., 2002). Other regulators of adipocyte metabolism include the prostaglandins, which may promote or inhibit adipogenic conversion depending on the type of prostaglandin. For example, PG-D2 and its 15-deoxy-J2 derivatives stimulate adipogenesis, perhaps via acting as PPARγ ligands (Kliewer et al., 1995), whereas $PGF_{2\alpha}$ represses adipogenic conversion of preadipocytes of various preadipose cell lines and primary rat preadipocytes (Negrel et al., 1981; Vassaux et al., 1994). Prostacyclin also promotes adipogenesis perhaps because it is able to activate the 3 PPAR isoforms (α, γ, and γ; Brun et al., 1996; Hertz et al., 1996).

Nutritional Regulation of Adipocytes

Nutrients affect adipocyte size, although they may also have an impact on adipose precursor differentiation by effects on mammalian target of rapamycin or glycogen synthase kinase as discussed elsewhere in the review. The impacts of macro- and micro-nutrients are numerous and also mediated by other regulatory systems.

Adipose Tissue Fatty Acid Composition. Chemically, fatty acids may be classified into 3 categories: SFA, MUFA, and PUFA. The most common SFA in meat products are myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0). Major MUFA include palmitoleic acid (16:1n-7) and oleic acid (18:1n-9), and major PUFA include linoleic acid (18:2n-6), linolenic acid (18:3n-3), and arachidonic acid (20:4n-6). Animal products are the main source of saturated fat in the human diet (Arab, 2003; Givens, 2005), and meat products with altered fatty acid profiles are considered value-added products in the marketplace. In addition to a reduction in the saturated:unsaturated fatty acid ratio, also known as the atherogenic index, interest in health-promoting lipids is growing. In particular, altering the oleic acid, linolenic acid, n-3, or CLA content of animal products has been suggested as a means to create healthier animal products. Because of biohydrogenation in the rumen, it is easier to change the fatty acid profile of pork by simple dietary means than beef. However, both can be manipulated (Raes et al., 2004). Although animal products with greater linolenic acid, or n-3, content may be desirable, the impact of these fatty acids on product quality is a concern due to the greater potential for oxidative damage, off-flavors, and, at least in pork, the effect on carcass firmness.

Exogenous Fatty Acids. The effects of dietary fat on adipose tissue have been reviewed previously (Azain, 2004). In practical diets, fat is added at less than 10% and typically less than 5% of the diet, for both ruminants and nonruminants. Dietary fat provides a substrate for lipid filling in adipocytes, but also has the potential to regulate adipocyte development (Ailhaud et al., 2006). In pigs and other nonruminants, dietary fat inhibits de novo fatty acid synthesis (**DNL**) and alters the fatty acid profile of adipose and other tissues such that it reflects the profile in the diet (Mourot and Hermier, 2001). Feeding unsaturated fat results in greater levels of unsaturation of lipids found in subcutaneous and intramuscular adipose tissue. Thus, it is possible to alter the fatty acid profile of pork such that it contains less saturated fat and greater amounts of n-3 or other PUFA (Irie and Sakimoto, 1992; Romans et al., 1995; Leskanich et al., 1997). The concern with such manipulation, however, is the potential negative impact on shelf-life or flavor (Van Oeckel et al., 1997; Wood and Enser, 1997). Recent studies in pigs fed linseed or fish oil before slaughter has not shown significant differences in fat oxidation in products with greater PUFA content (Corino et al., 2008; Haak et al., 2008). Whereas changes in shelf-life may not be an issue, the cost to produce animal products with improved or altered fatty acid profiles should be compared with consumer willingness to purchase premium products and the overall impact on the human diet. For example, Haak et al. (2008) compared the fatty acid profiles of muscle in pigs fed diets with animal fat, linseed (source of linolenic acid), or fish oil for the last 6 to 17 wk before slaughter. Total linolenic acid content per 100-g serving increased from 8 mg in tissue from pigs fed animal fat or fish oil to 19 mg in tissue from pigs fed linseed. Content of DHA + EPA was 5 mg/serving in the animal fat group and increased to 11 and 43 mg/serving with linseed and fish oil feeding, respectively. Similar observations were made by Corino et al. (2008) in pigs fed extruded linseed oil. Loin muscle content of linoleic acid increased from 9 mg/serving in the control group to approximately 30 mg in tissue from pigs feed diets with 5% extruded linseed for 4 to 10 wk before slaughter. Considering the American Heart Association recommendations (Kris-Etherton et al., 2002) for daily intake of linolenic acid are 1.5 to 3.0 g/d and those for EPA + DHA are in the range of 0.5 to 4 g/d, the impact of these changes on the total daily intake of n-3 fatty acids is minimal.

The effects of dietary fat on tissue fatty acid profiles are less clear in cattle and other ruminants. In contrast to nonruminants, rumen biohydrogenation makes the alteration of tissue fatty acid profiles more of a challenge. Biohydrogenation is particularly effective with 18-carbon fatty acids (linoleic and linolenic) that predominate in plant oils, but is less effective on longer chain PUFA, such as those found in fish oils (Scollan et al., 2001; Raes et al., 2004). Raes et al. (2004) reviewed studies that resulted in reductions in the n-6/n-3 ratio of lamb and beef as a result of feeding fish oil or fish meal (Raes et al., 2004). Whereas it is possible to alter the n-6/n-3 ratio in beef and lamb, the ratio of PUFA to SFA, which is less in ruminants (<0.10) than in pork (0.3 to 0.5), is resistant to changes due to diet (Raes et al., 2004).

Presently, there is interest in producing grass-fed beef, which indirectly represents an alteration of dietary fatty acid profile due to the increased content of

PUFA in forage. Beef from grass-feeding has less IMF and greater PUFA content than that of animals finished on concentrate diets (Leheska et al., 2008). Content of n-3 PUFA in grass-fed beef, expressed relative to total fatty acids, increased 5-fold relative to that from conventional production (1.07 vs. 0.19%). However, when one considers the reduction in total fat content (2.8 vs. 4.4%), the contribution per serving increases from less than 8 mg/serving to only 30 mg/serving.

Across meat animal species, a general observation is that as fat is added to the diet, DNL decreases. Numerous rodent studies demonstrate that PUFA have a greater ability to inhibit de novo lipogenesis than do SFA (Herzberg and Rogerson, 1988; Clarke, 2001). This is also observed in poultry (Sanz et al., 2000), but not in pigs (Smith et al., 1996) or cattle (Page et al., 2007), whereby the SFA source may have potencies that are similar or greater than those seen with unsaturated fat. Whereas dietary fat inhibits DNL, but not triacylglycerol synthesis, the effects are less clear on the overall rate of carcass fat deposition. Depending on the type of fat and how the diets are balanced for other nutrients, carcass fat has been shown to be either unchanged or greater in response to dietary fat in pigs (Pettigrew and Moser, 1991), poultry (Donaldson, 1985), and cattle (Zinn, 1989; Felton and Kerley, 2004). Fatty acids influence adipogenesis as precursors for the eicosanoids, as well as regulators of transcription. The effects of fatty acids seen in vitro or in rodent studies on adipogenesis have generally not been seen in livestock in response to feeding these same fats in vivo (Azain, 2004). As an example, there were no significant changes in gene expression in adipose tissue of young pigs feed fish oil, despite clear changes to vitro systems (Ding et al., 2000, 2003; Liu et al., 2005). The biohydrogenation of dietary fat in ruminants makes it even less likely that these fatty acids can affect adipose development in vivo. Nonetheless, the concentration of SFA can be decreased, and MUFA can be increased by gram quantities (e.g., Chung et al., 2006a), so changing these fatty acids in pork, beef, and lamb may have a significant impact on the nutritional value of meat.

CLA. Conjugated linoleic acid is one group of fatty acids that can have profound effects on adipose tissue. They were initially identified as anti-carcinogenic agents found in ground beef (Pariza and Hargraves, 1985), containing primarily the *cis*-9, *trans*-11 isomer. This isomer is an intermediate in the biohydrogenation pathway of converting linoleic acid (also α-linolenic acid) to stearic acid by rumen microorganisms (Kepler et al., 1966). Some CLA is absorbed by the small intestine, but the predominant source of *cis*-9, *trans*-11 CLA is Δ^9-desaturation of vaccenic acid (C18:1 *trans*-11; Piperova et al., 2002). Commercially produced CLA is a mix of many isomers with the 2 most prevalent being *cis*-9, *trans*-11 and *trans*-10, *cis*-12 and has been reported to have many health benefits, including anti-obesity effects (Mir et al., 2004). The anti-obesity effects of CLA have been attributed solely to the *trans*-10, *cis*-12 isomer (Hargrave et al., 2002).

Primarily the *cis*-9, *trans*-11 isomer of CLA is present in small quantities (~0.5 to 1% of total fatty acids) in ruminant fat (Wynn et al., 2006; D'Urso et al., 2008), but pasture feeding has proven to be an excellent method of increasing the CLA content in adipose tissue and muscle of beef (Mir et al., 2004; Noci et al., 2005), as well as in milk fat (D'Urso et al., 2008; Khanal et al., 2008). The dietary addition of high-PUFA oils such as sunflower, soybean, linseed, or fish oils also increases the production and incorporation of vaccenic acid and *cis*-9, *trans*-11 CLA in ruminants (Chouinard et al., 2001; Mir et al., 2002; Sackmann et al., 2003; Bouattour et al., 2008). Ruminants fed rumen-protected, or abomasally infused, CLA have increased concentrations of CLA in meat (Gillis et al., 2004; Wynn et al., 2006), and milk (Loor and Herbein, 1998; Chouinard et al., 1999), with the CLA isomer profile in the meat reflecting the profile of the supplemented source. The fatty acid profiles of monogastric species are easier to manipulate because they incorporate dietary fatty acids readily, and a mixed isomer preparation of CLA has successfully been incorporated into the tissues of broiler chickens (Badinga et al., 2003), pigs (Demaree et al., 2002), and several fish species (Kennedy et al., 2007; Valente et al., 2007a,b), resulting in detectable concentrations of both *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA. Unfortunately, use of CLA as a feed additive is currently not approved for food animals. Estimated costs for feed-grade CLA oil are likely to be 5-fold greater than current prices for other fats, so the cost of supplementing CLA into animal diets may be prohibitive. As with n-3 fatty acids, feeding CLA to nonruminants might increase meat quality, but given the target intake of 3 to 5 g/d that is the extrapolated dose needed to reproduce the anti-carcinogenic effects seen in rodents (Ip et al., 1994), the overall impact of CLA-enriched pork on the total daily consumption of this class of fatty acids is minimal (Azain, 2004).

The other primary reason for CLA supplementation to livestock is for its fat-reducing properties (Mir et al., 2004). Conjugated linoleic acid is often supplemented as a mixed isomer preparation, but only the *trans*-10, *cis*-12 isomer of CLA possesses these anti-obesity effects, which have been most consistent in rodents (Navarro et al., 2003), although decreases in body fat have also been observed in meat animal species including chickens (Szymczyk et al., 2001) and rabbits (Corino et al., 2002). These changes in body composition appear to involve repartitioning of energy stores away from body fat and toward lean muscle mass (Azain, 2003). Additionally, CLA-fed pigs have been reported to have less backfat but more intramuscular fat or marbling (Dugan et al., 1997). These results have not been consistent, however, and may depend upon sex, BW, genetics, degree of fatness of the pigs, or a combination of these (Azain, 2003). Interestingly, CLA supplementation of

ruminant animals has not resulted in altered body fat stores (Gillis et al., 2004; Wynn et al., 2006), but reportedly reduced the percentage of milk fat (Baumgard et al., 2000, 2002). This effect appears to be due to the inhibition of DNL in the mammary gland due to the prevention of SREBP-1c (Bauman et al., 2008).

The mechanism by which CLA alters body fat is largely unknown, but several potential pathways have been identified in rodent or in vitro models. Briefly, CLA causes a negative energy balance by reducing energy intake, increasing energy excretion, and stimulating energy expenditure via heat loss. These changes appear to be the result of altered fatty acid turnover. In addition, CLA causes increased lipolysis and β-oxidation and inhibits fatty acid synthesis and uptake. Many of these actions appear to be induced through altered gene expression, caused by the activation of the mitogen-activated protein kinase kinase/extracellular regulated kinase, PPARγ, and mammalian target of rapamycin signaling pathways. Furthermore, CLA blocks adipose tissue development by inhibiting preadipocyte proliferation and differentiation, inducing de-differentiation of mature adipocytes, and stimulating programmed cell death of adipogenic cells (House et al., 2005).

Experiments with pigs or porcine cells have not all been consistent with the results outlined above. For example, adipose tissue from pigs did not respond to CLA treatment with increased lipolysis (Jose et al., 2008), although this may be an effect of the base diet because CLA-induced lipolysis was detected only in mice fed low PUFA diets (Hadenfeldt et al., 2005). The effect of CLA on porcine cells in vitro has not corresponded with mouse or human cells. Indeed, CLA did not affect proliferation of porcine primary SV cells (McNeel and Mersmann, 2003; Zhou et al., 2007), and Ding et al. (2000, 2002) reported increased differentiation in CLA-treated porcine primary cultures. This effect may be depot-specific as porcine SV cells isolated from subcutaneous adipose tissue responded to CLA treatment with reduced adipocyte-specific gene expression and lipid accumulation, but SV cells isolated from intramuscular adipose tissue had greater adipocyte gene expression following CLA treatment (Zhou et al., 2007). A likely mechanism by which CLA influences preadipocyte differentiation is by interacting with PPARγ. Analysis with transfected porcine cells indicates that CLA isomers activate PPARγ, as measured by reporter assays and increased target gene expression (Ding et al., 2000; Belury et al., 2002). This is in contrast to results obtained with 3T3-L1 cells, where CLA prevented ligand-induced activation of PPARγ (Brown et al., 2003; Granlund et al., 2003). Interestingly, the PPARγ protein is normally found almost exclusively in adipose tissue (Chawla and Lazar, 1994); therefore, an increase in PPARγ expression in muscle of pigs that may play a role in increased intramuscular fat (Meadus et al., 2002). Clearly, further research in CLA-altered fat stores in livestock species is needed. An understanding of the mechanism(s) of action of CLA isomers would also provide key insight into adipose tissue regulation in general.

Other Compounds. An exciting area of research has been initiated whereby other nutrients have shown potential in altering the cellularity of adipose depots. For example, feeding diets low in vitamin A or vitamin A restriction for long periods in beef and dairy steers increased intramuscular or marbling adipose deposition without influencing other adipose depots (Gorocica-Buenfil et al., 2007a,b,c). Intramuscular fat cell size was not influenced by dietary vitamin A, whereas an apparent increase in intramuscular fat cell number was observed. These studies indicate that feeding low vitamin A diets for long periods may represent a viable way to enhance intramuscular fat or marbling deposition because yield grade, animal health, feedlot performance, and carcass weight were not adversely influenced (Gorocica-Buenfil et al., 2007a,b). However, a recent study of long-term vitamin A restriction in beef cattle failed to show an influence on marbling deposition (Gorocica-Buenfil et al., 2008). Therefore, further study is necessary to evaluate the reproducibility of the influence of low vitamin A diets on marbling fat deposition. Similarly, research on other (potential) bioactive compounds is needed in the future.

Modifiying Fatty Acid Composition During Adipocyte Differentiation. Fatty acids endogenously expressed in adipocytes have a profound effect on beef quality and nutritional value. This is especially true for oleic acid (18:1n-9). Early research demonstrated that the concentration of oleic acid in beef is positively correlated with overall palatability (Waldman et al., 1968; Westerling and Hedrick, 1979). This may be related to fat softness because beef lipids enriched with oleic acid have lower melting points (Smith et al., 1998b; Wood et al., 2004; Chung et al., 2006b). There also is a growing body of information to indicate that increasing the intake of oleic acid (usually as olive or canola oil) reduces risk factors for metabolic disease in human subjects (Grundy et al., 1988; Kris-Etherton et al., 2002). Oleic acid is the most abundant fatty acid in US beef (Waldman et al., 1968; Westerling and Hedrick, 1979), and it is especially elevated in beef from Japanese Black (Sturdivant et al., 1992) and the closely related American Wagyu (May et al., 1993; Chung et al., 2006b) and Korean Hanwoo (Jung and Choi, 2003). Stearic acid (18:0) is 1 of the 2 primary fatty acids (the other being palmitic acid, 16:0) that dictate fat hardness (Smith et al., 1998b; Wood et al., 2004; Chung et al., 2006b), so any dietary or production factor that increases the conversion of stearic acid to oleic acid will increase fat softness. The enzyme responsible for the conversion of all SFA to their respective MUFA, as well as *trans*-vaccenic acid to rumenic acid (*cis*-9, *trans*-11 CLA), is Δ^9 desaturase.

In the United States, there is no economic incentive to produce beef that has greater oleic acid content. Un-

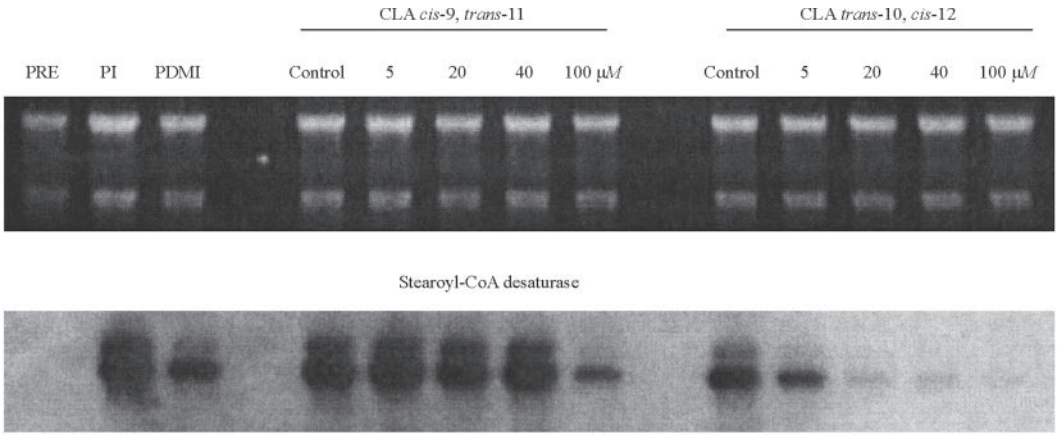

Figure 2. Stearoyl-CoA desaturase gene expression in bovine preadipocytes at confluence (PRE); differentiated in the presence of 5 μ*M* pioglitizone, 10 μg/mL of insulin, and Dulbecco's modified Eagle medium (PI); or differentiated with PI plus 1 μg/mL of dexamethasone (PDMI). In lanes 4 to 10, preadipocytes were differentiated for 7 d with PI in the presence of *cis*-9, *trans*-11 or *trans*-10, *cis*-12 CLA. Derived from data in Chung et al. (2006a). Lipid filling and the synthesis of MUFA also were depressed by *trans*-10, *cis*-12 CLA but not *cis*-9, *trans*-11 CLA (Chung et al., 2006a).

der the USDA beef grading system, carcass value is determined primarily by the abundance of marbling adipose tissue (USDA, 1997). However, in Japan, fat softness, whiteness, and marbling abundance all are important components of beef carcass quality grade (JMGA, 1988). The Japanese beef export market is worth several billion dollars, so investigators in the United States, Korea, and Australia are focusing their research on the modifying Δ^9 desaturase catalytic activity.

In cattle and pigs, Δ^9 desaturase catalytic activity is especially high in subcutaneous adipose tissue (Smith, 1995). Over 20 yr ago, Casimir and Ntambi (1996) demonstrated that expression of the Δ^9 desaturase gene, stearoyl-CoA desaturase (**SCD**), increases immediately preceding lipid filling in murine 3T3-L1 cells. Virtually identical results have been demonstrated for bovine preadipocytes (Figure 2; Chung et al., 2006a) in which SCD mRNA was undetectable in pre-confluent cells but highly abundant after 7 d of exposure to insulin ± pioglitizone. The SCD gene expression was depressed slightly by dexamethasone (PDMI in Figure 2) and by high concentrations of rumenic acid. However, even very low concentrations of *trans*-10, *cis*-12 CLA depressed SCD gene expression, which was reflected in a large reduction in the synthesis of MUFA by the preadipocytes (Chung et al., 2006a).

Fatty Acid Composition of Adipose Tissue at Different Stages of Growth in Beef Cattle. Adipose tissue fatty acids typically become less saturated between weaning and slaughter in cattle that are fed a corn-based diet (Huerta-Leidenz et al., 1996; Chung et al., 2006b). The MUFA:SFA ratio increases from 0.66 to 0.86 between weaning and 16 mo of age, primarily due to an increase in oleic acid (S. B. Smith, unpublished data). There is no increase in the MUFA:SFA ratio between weaning and 12 mo of age in cattle fed pasture-based diets. The lesser MUFA:SFA ratio in pasture-fed steers, relative to corn-fed steers, suggests that some component of pasture diets causes a depression in Δ^9 desaturase activity. This was demonstrated in sheep fed concentrate- and forage-based diets (Daniel et al., 2004). There was a greater accumulation of oleic acid and a greater ratio of SCD to acetyl-CoA carboxylase mRNA in adipose tissue of concentrated-fed sheep than in forage-fed sheep. There is a possibility that forage diets depress SCD gene expression through an elevation of *trans*-10, *cis*-12 CLA during forage or pasture feeding.

In many breed types, there is a nearly linear increase in marbling (or intramuscular lipid) with time on a finishing diet (Figure 3), consistent with an increase in adipose tissue MUFA and Δ^9 desaturase activity. Measuring Δ^9 desaturase activity in animals is technically difficult and requires large quantities of adipose (up to 50 g; Yang et al., 1999). Although smaller quantities can be used, such as that obtained from dissection of marbling adipose tissue (Archibeque et al., 2005), the degree of accuracy is reduced greatly. A relatively accurate and reproducible estimator of Δ^9 desaturase catalytic activity is the ratio of palmitoleic acid (16:1n-7) to stearic acid (Figure 4; Smith et al., 2006). There is virtually no palmitoleic acid in the diets of livestock species, and its presence in adipose tissues or beef is dependent entirely on endogenous synthesis. American Wagyu or Angus cattle fed high-corn diets have high Δ^9 desaturase activity (Chung et al., 2007) and high palmitoleic:stearic acid ratios (Figure 4).

Expression of the SCD gene increases profoundly between weaning and 12 mo of age in subcutaneous adipose tissue of Angus steers (Figure 5; Martin et al., 1999). Similarly, Lee et al. (2005) observed peak SCD mRNA at 12 mo of age in muscle from Hanwoo steers. Δ^9 Desaturase activity appears to be essential for subsequent development of lipogenic capacity of subcutaneous adipose tissue in growing steers. A MUFA:SFA ratio of nearly 1.2 can be achieved in Angus steers fed

a hay-based diet for 16 mo postweaning to 24 mo of age (Chung et al., 2006b). However, cattle fed in Australia in excess of 400 d achieved a MUFA:SFA ratio of only 0.77, and stearic acid is markedly elevated in their adipose tissue lipids (Smith et al., 1998b). Japanese Black cattle fed roughage/grain diets can attain MUFA:SFA ratios approaching 2:1 (Sturdivant et al., 1992; Chung et al., 2006b), consistent with the genetic predisposition of this breed type to have greater adipose tissue SCD gene expression than conventional breed types (Chung et al., 2007).

Influence of Adipocytes on Other Tissues

Adipose tissue is an endocrine organ in which adipocytes secrete several factors that affect other tissues (Kokta et al., 2004). Regulatory release mechanisms, action at the level of target tissues or cells, and systemic impact are presently being defined in meat animals. This area of research is expected to provide significant knowledge regarding the importance of preadipocytes and adipocytes.

Adiponectin. Adiponectin is secreted primarily by adipocytes in many species including the pig (Lord et al., 2005; Dai et al., 2006). Adiponectin circulates at elevated (μg/mL) serum concentrations (Hotta et al., 2000, 2001) as a trimer, hexamer, high molecular weight multimer, and as a carboxyl terminal cleavage peptide (globular form; Kobayashi et al., 2004) and exhibits structural homology with collagen VIII and X and complement factor C1q. Recently, 2 different receptors for adiponectin, AdipoR1 and AdipoR2 (Yamauchi et al., 2003), were identified and are expressed in pig adipocytes (Dai et al., 2006). Adiponectin suppresses the incorporation of glucose carbon into lipid in primary pig adipocytes (Jacobi et al., 2004). Recently, Hu et al. (2007a) determined that administration of recombinant adiponectin to diabetic swine improved insulin sensitivity and enhanced glucose clearance.

Leptin. As with adiponectin, leptin is produced predominantly in the adipose tissue (Zhang et al., 1994; Bidwell et al., 1997; Ramsay et al., 1998). It is secreted into the blood and thereafter reaches a myriad of target cells in the brain and peripheral tissues. Leptin acts somewhat acutely as a nutrient sensor, but circulating concentrations also reflect adipose mass in pigs (Jacobi et al., 2004), rodents (Frederich et al., 1995; Maffei et al., 1995), and humans (Maffei et al., 1995). Whereas leptin clearly functions through central mechanisms to regulate caloric intake and energy expenditure, there is convincing evidence of its direct effects on peripheral tissues. Exposure to leptin inhibits lipogenesis in primary porcine adipocytes and in adipocytes derived from SV cells. Although the underlying mechanism is not known, it encompasses a disruption of insulin-stimulated lipogenesis (Ramsay, 2003). In some models, leptin also acts to suppress the inhibition of β-receptor-mediated lipolysis by insulin (Ramsay, 2001) and reduces insulin-induced glucose transport, lipogenesis, or both (Ramsay and Richards, 2004). In the absence of insulin, leptin directly stimulates lipolysis in cultured pig adipocytes (Ajuwon et al., 2003). Mechanistically, the detailed regulation of lipolysis by leptin is not well characterized in meat animal species.

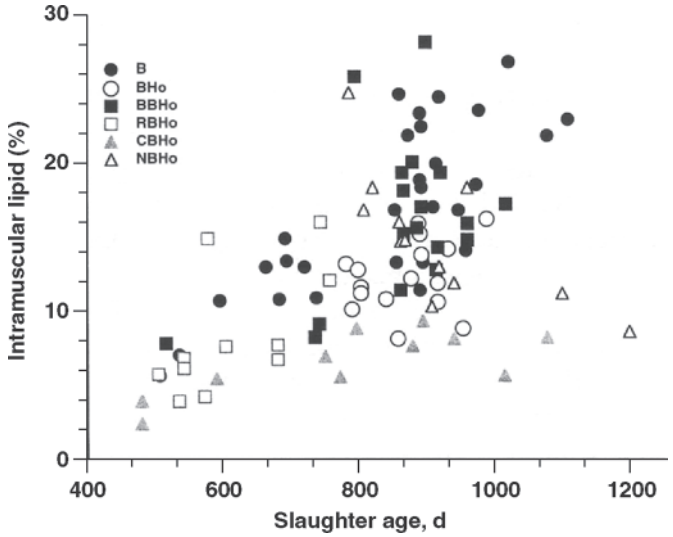

Figure 3. Percentage intramuscular lipid as a function of slaughter age. Abbreviations for breed types: B = Japanese Black; BHo = Japanese Black × Holstein; BBHo = Japanese Black × Japanese Black/Holstein; RBHo = Japanese Brown × Japanese Black/Holstein; CBHo = Charolais × Japanese Black/Holstein; NBHo = Japanese Shorthorn × Japanese Black/Holstein. All cattle were fed a high concentrate finishing diet. Reprinted with permission from Zembayashi et al. (1999).

Resistin. Resistin is a cysteine-rich, adipocyte-derived protein that has been linked to the development of insulin resistance (Steppan et al., 2005). The potential use of resistin in livestock species is unknown because limited information is available. However, resistin mRNA has been identified in the adipose tissue and mammary gland of lactating and dry dairy cows (Komatsu et al., 2003). Resistin expression in the adipose tissue increased during the transition period while expression in the mammary gland decreased. It was therefore speculated that resistin may play a role in directing the site of glucose uptake from the adipocyte to the mammary gland during peak lactation. Porcine resistin has also been identified, and mRNA has been detected in adipose tissue (Dai et al., 2006). Resistin mRNA expression increased with age of the pig and was greater in obese pigs than in lean pigs (Cheng et al., 2004). Resistin mRNA was detected in both the adipocyte and SV fractions of the adipose tissue, although the expression level was low compared with that found in leukocytes (Dai et al., 2006). The role of porcine resistin in insulin resistance has not been investigated, but a SNP in the resistin gene has been correlated with several pork quality traits including marbling and total lipid percentage (Otieno et al., 2005). Further research is clearly needed to determine the expression pattern and role of resistin in both preadipocytes and adipocytes of livestock species.

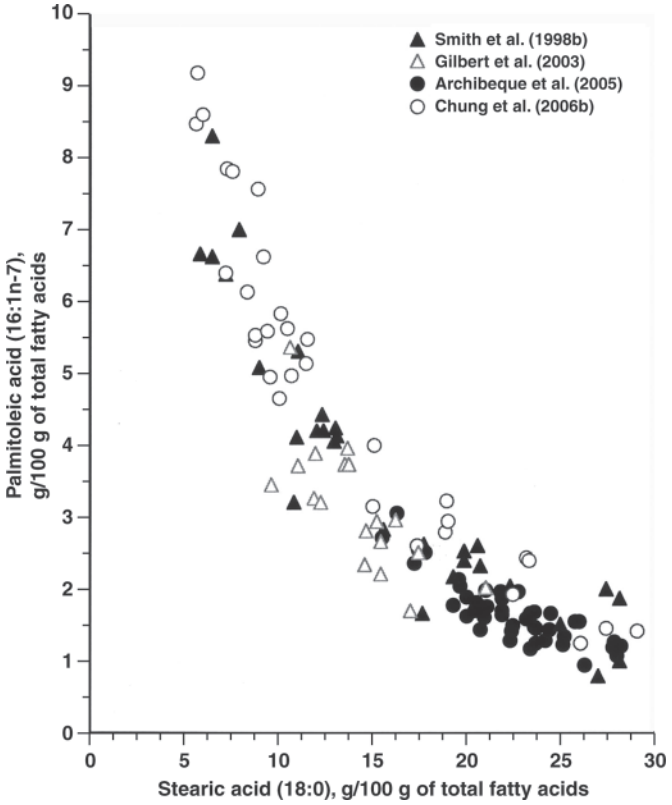

Figure 4. Relationship between stearic acid (18:0) and palmitoleic acid (16:1n-7) in subcutaneous adipose tissue lipids of cattle raised in Australia and Japan (Smith et al., 1998b) or in the United States (Gilbert et al., 2003; Archibeque et al., 2005; Chung et al., 2006b). Cattle raised in Australia were crossbred Murray Grey, Angus, and Grey Brahman steers fed a grain-based diet for a minimum of 400 d, whereas those raised in Japan were Murray Grey and Japanese Black fed for approximately 570 d. Cattle raised in the United States were Brangus (Gilbert et al., 2003), Angus (Archibeque et al., 2005; Chung et al., 2006b), or American Wagyu (Chung et al., 2006b). The relationship between palmitoleic acid and stearic acid provides an index of Δ^9 desaturase activity; greater Δ^9 desaturase activity is seen in samples with high palmitoleic acid and low stearic acid (Yang et al., 1999).

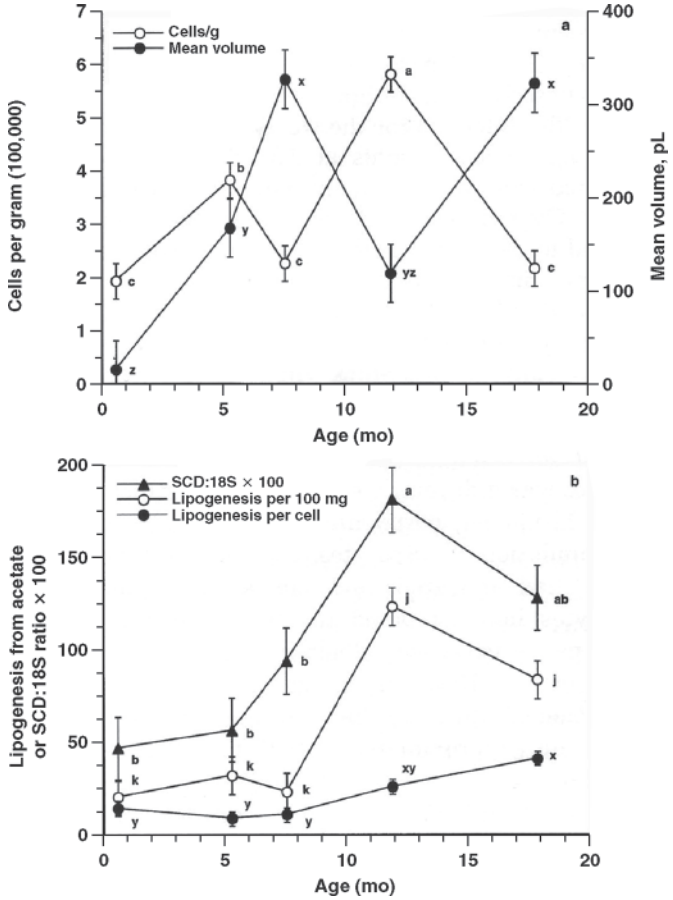

Figure 5. Changes in cellularity, lipogenesis, and stearoyl-CoA desaturase (SCD) gene expression during growth in preweaning (2.5 wk to 7.5 mo) and postweaning Angus steers. (a) Mean values for number of adipocytes per gram of adipose tissue and adipocyte volumes. (b) Lipogenesis and SCD gene expression. Overall SE of the means are affixed to the symbols for each item. [a–c,jk,xy]Values within a measurement with the same letters were not different ($P > 0.05$). Reprinted with permission from Martin et al. (1999).

Genes That Regulate Adipocyte Activity

During the last 2 decades, many genes have been identified that are directly or indirectly involved in the regulation of adipogenesis in mammalian species including pig and cattle (Fernyhough et al., 2007; Bai et al., 2008; Taniguchi et al., 2008b). Genes encoding transcription factors including PPAR and C/EBP have been identified that directly influence fat cell development both in vitro and in vivo (Rosen et al., 2000; Fernyhough et al., 2007), by encoding transcriptional factors that regulate gene expression of downstream genes that are typically involved in lipid and fatty acid metabolism. These factors do not work completely independently but interact functionally in several important ways. The PPARγ 2 has been found to regulate the expression levels of many genes that are involved in adipocyte differentiation including genes involved in lipid accumulation and metabolism such as Ap2, collagen type I receptor/thrombospondin receptor (CD36), lipoprotein lipase, perilipin, and phosphoenolpyruvate carboxykinase (Rosen et al., 2000; Fernyhough et al., 2007). In addition, PPARγ expression is affected by other transcription factors such as Kruppel-like zinc finger family (Mori et al., 2005), Krox-20 (Chen et al., 2005), zinc-finger transcription factors (Tong et al., 2000), repressor proteins (TCF/Lef; Kennell et al., 2003), the transcription factor E2F (Fajas et al., 2002), and mothers against DPP homolog (SMAD; Choy and Derynck, 2003) for early development of adipogenesis. A recent study by Park et al. (2008) reported that the overexpression of Id proteins, a helix-loop-helix domain transcription factor, in 3T3-T1 preadipocytes promoted the expression of PPARγ and enhanced the morphological differentiation and lipid accumulation (Park et al., 2008). Although the transcriptional factor PPARγ plays a central role in adipogenesis, the complicated transcriptional pathways that regulate its expression remain poorly understood in meat animals (Fernyhough et al., 2007) and need further investigation.

The C/EBP-α protein is another important transcription factor that helps regulate adipogenesis in sev-

eral species (Kim et al., 2007). However, several adipocyte cell lines fail to express C/EBP-α and exhibit reduced insulin sensitivity despite an apparent adipogenic phenotype. Other genes regulate adipogenesis by influencing insulin uptake, increased triglyceride accumulation and GPDH activity (Phloretin; Hassan et al., 2007), adiponectin gene expression (Kim et al., 2006), glucose uptake [**GLUT-4** (Fernyhough et al., 2007), and GLUT-4 enhancer factor (Sparling et al., 2008)], glucose and lipid metabolism with AMP-activated protein kinase activator 5-aminoimidazole-4-carboxamide ribonucleoside (Dagon et al., 2006), enhancing PPARγ expression (Saito et al., 2008), insulin secretion, glucokinase gene transcription, and β cell proliferation by Wnt signaling to promote fat mobilization (Bai et al., 2008), regulator of circadian rhythm in mature adipocytes [brain and muscle Arnt-like protein-1 (BMAL1, MOP3, or Arnt3; Shimba et al., 2005)], and many others. The unique regulation of downstream genes in bovine preadipocytes suggests that the regulation pathways may be species-specific (Tan et al., 2006; Taniguchi et al., 2008b). Further work is required to understand the complete regulation pathway through PPAR isoforms, C/EBP, as well as other gene families in meat animals.

Adipose Tissue Transcription and Proteomic Profiling of Adipogenesis

Transcriptome Profiling. The precise patterns of differentially expressed genes ultimately direct a particular cell toward a given lineage, and many of these differentially expressed genes are regulated during the earliest stages of cell differentiation. Global gene expression patterns have been intensively studied and modeled using the 3T3-L1 preadipocyte cell line and DNA microarray analysis (Hackl et al., 2005). The initial 24-h period in preadipocyte conversion into a lipid-assimilating adipocyte is complex, as shown by 285 cDNA/EST having at least a 5-fold change in expression levels during this time course (Burton et al., 2002). The identified differentially expressed genes may well represent novel adipogenic mediators. For example, Wdnm1-like, a distant member of the whey acidic protein/4-disulfide core family was identified from DNA microarray analysis of 3T3-L1 and ScAp23 cells as a gene with possible roles in remodeling of the extracellular milieu during white and brown adipose differentiation (Wu and Smas, 2008). Genomic data can be correlated with a particular phenotype, when large numbers of transcripts are analyzed for differentially expressed genes and interactions among genes. A very recent study using microarray analysis also identified the changes in adipocyte gene expression patterns when the diet was changed in the obese mice (Miller et al., 2008).

The interactions among genes in adipocyte differentiation in livestock species remain unclear (Fernyhough et al., 2007). Hishikawa et al. (2005) reported gene expression differences in subcutaneous and visceral fat tissues among cattle, mouse, and pig, and demonstrated that expression profiles between tissue types were different and fat accumulation mechanisms were different among animal species. This may be associated, in part, with differences in lipid metabolism among these 3 species (Fernyhough et al., 2007, 2008; Taniguchi et al., 2008b,c). Recent studies using a novel in vitro model of cattle adipocytes showed that PPAR-γ and SREBP-1 expression during bovine perimuscular fat preadipocyte differentiation by transcriptional activation of SREBP-1c and PPAR-γ led to upregulation of 6 downstream genes (Taniguchi et al., 2008b). Moreover, a bovine-specific oligo-DNA microarray containing 70-mer oligos representing 8,329 genes from *Bos taurus* genome (Operon Biotechnologies Inc., Huntsville, AL) is being used to evaluate the global overview of differentially expressed gene expression (Taniguchi et al., 2008a). Results from this study showed a total of 100 significantly differentially expressed genes between differentiated and nondifferentiated (control) cells. Most of the differentially expressed genes were observed in DNA/RNA binding and catalytic activity at each time point in up- or downregulation. The proportions of differentially expressed genes in binding activity moderately increased in upregulated genes as the time elapses (27.3% on d 2, 28.9% on d 4, and 29.4% on d 8), whereas decreases in downregulated genes were observed in 20.3% of genes on d 2, 19.0% of genes on d 4, and 18.7% of genes on d 8 (Figure 6). The similar characteristics of gene expression profiles were observed in a study of bovine bone marrow-derived preadipocyte development (Tan et al., 2006), suggesting the results reflect a genetic aspect of differentiating bovine preadipocytes. Use of quantitative real-time PCR analysis of selected genes from microarray analysis validated that typical adipogenic genes, including DGAT1, FABP3, FABP4, FASN, and PPAR-γ, were upregulated during early differentiation in the bovine-derived preadipocytes. Recently, Taniguchi et al. (2008c) reported a total of 360 differentially expressed genes were detected between adipose tissues from beef cattle, with low and high backfat thickness (Figure 7). Most of the differentially expressed tissue genes were found in functions of binding (48.2%) and catalytic activity (32.3%), whereas those associated with other molecular function were less than 5%. Among these genes, 45 out of 360 DE genes were found to be involved in 82 pathways with some of them capable of cross-talk (Taniguchi et al., 2008c). These collective results, in part, suggest that the bovine preadipocyte system may be a viable in vitro model for molecular adipogenesis studies and can be used to understand adipogenesis in livestock.

Proteome Profiling. Recent attempts using gene expression profiling to elucidate molecular mechanisms of adipocyte differentiation have identified hundreds of genes involved in several biochemical pathways and cellular and molecular signaling. Unfortunately, expres-

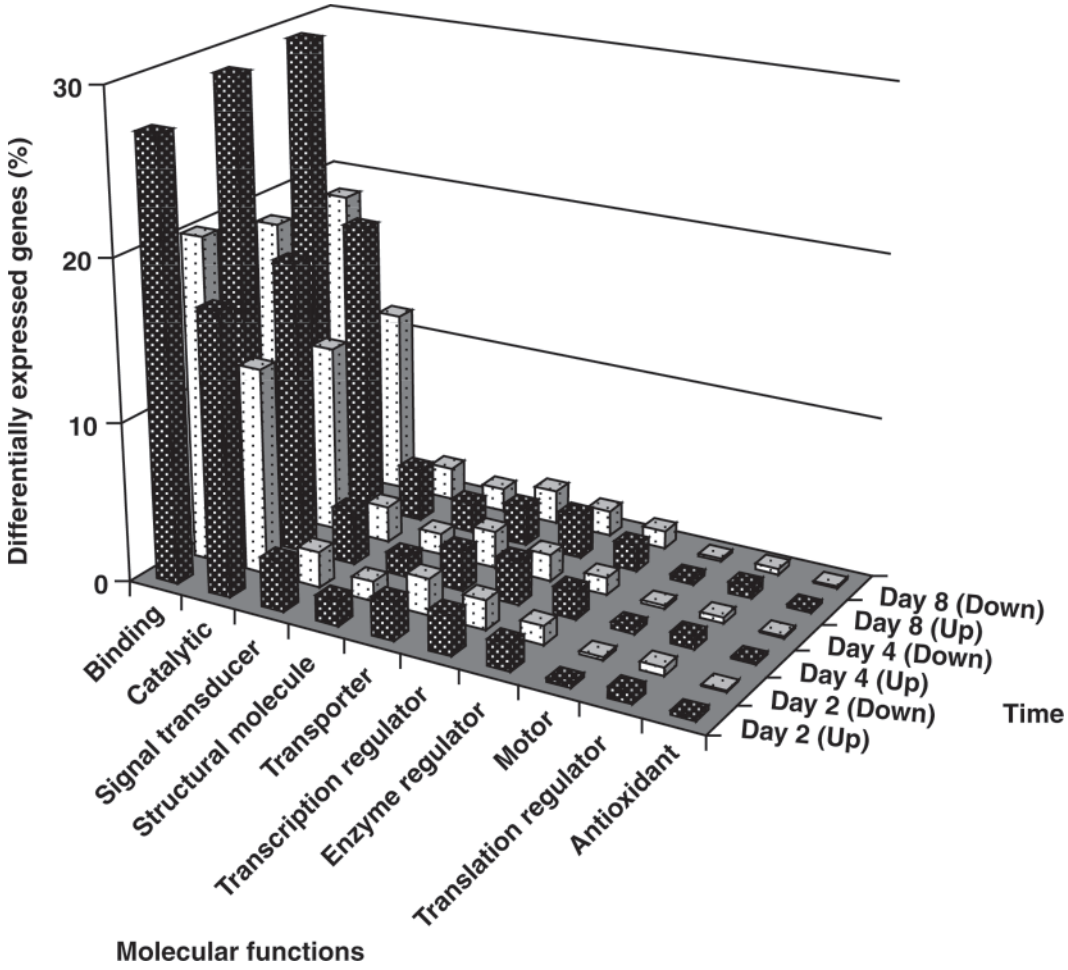

Figure 6. Differentially expressed gene ontology analysis during bovine perimuscular fat preadipocyte differentiation. The x-, y-, and z-axes indicate molecular functions, time, and percentages of the differentially expressed genes, respectively. Brackets show up- or downregulation in each time point as described in Taniguchi et al. (2008b).

sion levels of mRNA do not always parallel the levels of protein expression from any particular gene. Moreover, protein turnover and posttranslational modifications, essential for cellular behavior, are not represented by the information obtained from DNA microarrays. Consequently, a broader understanding of adipogenesis requires independent examination of protein expression and protein function complementing mRNA expression analyses. The development of proteomics using 2-dimensional gel electrophoresis mass spectrometry or protein arrays (Bertone and Snyder, 2005; He et al., 2008) allows researchers to quantitatively examine global changes in protein expression profiles and potential impact on subsequent cellular pathways (Sauer et al., 2005). This method has been determined of value in numerous recent studies using 3T3-L1 preadipocytes (Renes et al., 2005; Rahman et al., 2008).

Combined Approach. Combining proteomic and transcriptomic strategies to understand molecular mechanisms of 3T3-L1 cell adipogenesis has recently been attempted. Wilson-Fritch et al. (2003) revealed that a 20- to 30-fold increase in the concentration of numerous mitochondrial proteins was observed during adipogenesis, as determined by mass spectrometry and database correlation analysis. Their results showed increases in the expression of many nucleus-encoded mitochondrial genes during adipogenesis and that these genes could be regulated by the actions of insulin sensitizers.

Adipose Tissue Transcriptional Profiling of Porcine Adipose Tissue

Fetal and Neonatal Adipose Tissue. Transcription profiling and proteomic studies have been used to discover the expression of many unique and unexpected genes and proteins in human and rodent adipose tissue with considerable relevance to human health. Developing pig adipose tissue serves as a biomedical model because the pig is used extensively as a model in associated lipid metabolism studies (Nafikov and Beitz, 2007). Over 40 genes encoding known adipose tissue-secreted proteins were detected in fetal SV cell cultures and fetal and neonatal adipose tissue microarrays. Additionally, 180 genes encoding nonsecreted regulatory factors such as transcription factors, nuclear receptors, enzymes, and other regulatory proteins were detected. Ten secreted protein genes and numerous regulatory

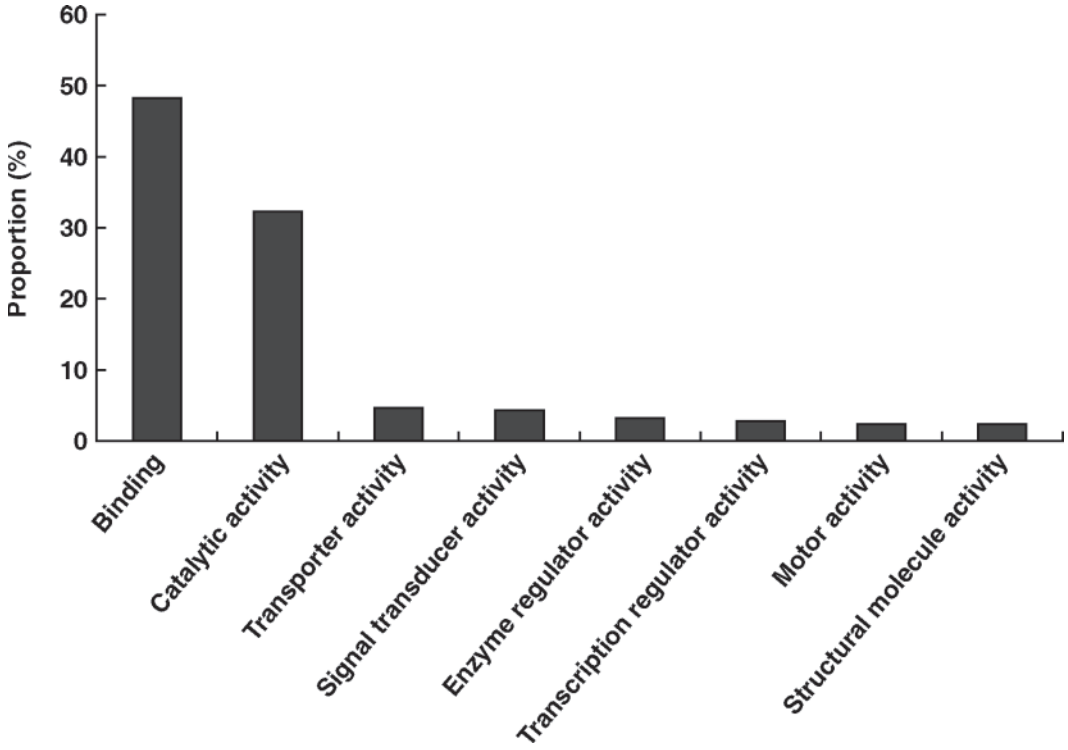

Figure 7. Ontology analysis of 360 differentially expressed genes in bovine subcutaneous adipose tissue. The x- and y-axes indicate percentages of the differentially expressed genes and molecular functions, respectively.

factor genes not known to be expressed by adipose tissue were detected in neonatal adipose tissue and fetal SV cell culture microarrays. Twenty adipose tissue-secreted proteins were detected using both gene microarray and the proteomic assays including apolipoprotein-A1, brain-derived neurotrophic factor, and IGFBP-5. These studies demonstrated that many key regulatory proteins and major secreted proteins were expressed much earlier than expected during adipose tissue development (Hausman et al., 2006).

Adipose Tissue from Growing Animals. Because age-associated changes in global gene expression in adipose tissue have not been examined in any species, custom cDNA microarray studies of adipose tissue from growing pigs were initiated. Gene expression ratios revealed little age-associated change in expression of many cytokines, apolipoproteins, IGFBP, hormones, growth factors, and regulatory factors—several including GH and leptin receptors in numerous adipose depots (Hausman et al., 2007, 2008). However, real-time reverse transcription-PCR assays showed age-associated increases in adipose tissue expression of heat shock transcription factor 1, connective tissue growth factor, 15-oxoprostaglandin 13-reductase, adiponectin, and leptin. Age-related decreases in adipose tissue expression of IL-1B, regulated upon activation, T-cell expressed and secreted protein, neuropeptide Y (**NPY**), and prohibitin 2 were also confirmed (Hausman et al., 2007, 2008). Furthermore, the expression of several genes was demonstrated in pig adipose tissue for the first time including NPY, ciliary neurotrophic factor, heat shock transcription factor 1, regulated upon activation, T-cell expressed and secreted protein, IL-1B, IL-1 receptor antagonist, and apolipoprotein-A1 (Hausman et al., 2007, 2008). Distinct patterns of relative gene expression were evident within apolipoproteins, IL, IGFBP, TGF β family members, and NPY receptors in adipose tissue from growing pigs (Hausman et al., 2007, 2008). Comparing outside subcutaneous and middle subcutaneous (**MSQ**) patterns of gene expression within apolipoproteins, IL, interferons, and transforming growth factor β family members distinguished these depots in growing pigs. These studies also demonstrated that expression of major cytokines, apolipoproteins, and regulatory factors are influenced by age and depot.

Several negative and positive associations between leptin and expression of other genes from adipose tissue of growing gilts were observed (Hausman et al., 2007, 2008). Significant linear regressions between individual pig leptin gene expression values and individual expression values of several regulatory factors and several cytokines were demonstrated (Figures 8 and 9). Of 12 interleukins examined, only IL-15 expression was positively associated with leptin expression (Figure 9). Regulatory genes shown to be associated with leptin gene expression have not been studied to any extent in meat animal adipose tissue but do have roles in mouse rodent adipogenesis. Future study of these regulatory genes and cytokines could lead to new insight on regulation of leptin and adipogenesis in meat animals.

Influence of Feed Restriction and Fasting in Prepubertal Pigs. The influence of short-term feed restriction on adipose tissue function in the prepubertal period was examined with custom cDNA microarray

analysis of 4 adipose tissue depots from ovariectomized gilts fed a restricted (33% of control diet) for 8 d (Hart et al., 2007). The effects of feed restriction on adipocyte gene expression were clearly depot-dependent with the greatest number of genes significantly affected in the perirenal fat depot and the least in the MSQ. Regardless of adipose depot, expression of genes involved in fatty acid metabolism, stearoyl-CoA desaturase, PPARγ, lipoprotein lipase, and malate dehydrogenase, decreased in response to feed restriction, whereas several major markers of adipocyte development were not changed. Furthermore, feed restriction prevented backfat gain, and adipocyte function was altered as evidenced by upregulation of thyroid hormone receptor-α in perirenal, leaf, and mesenteric fat depots in feed-restricted animals (Barb et al., 2009), which coincided with elevated thyroxine concentrations in restricted pigs (Hart et al., 2007). The influence of fasting (Lkhagvadorj et al., 2008) and feed restriction (Lkhagvadorj et al., 2006) in prepubertal gilts has also been studied with large porcine Affymetrix arrays to identify regulatory adipose tissue metabolic pathways. Gilts were feed restricted to 80% of maintenance for 7 d or fasted for 3 d and MSQ sampled. Over 2,500 and 7,000 adipose tissue genes were differentially expressed in response to feed restriction and fasting, respectively. As expected, lipid biosynthetic genes such as SREBP-1c, fatty acid synthase, aconitase-1, acetyl CoA carboxylase α, and acetyl CoA synthase were downregulated in adipose tissue. Approximately 21% of all downregulated genes in adipose tissue were directly regulated by SREBF1, indicating that it may play a key role in responding to food deprivation (Lkhagvadorj et al., 2008). These studies identified multiple genes and metabolic pathways important to the regulation of feed efficiency and feed intake in pigs. Furthermore, genes were identified that are involved in maintaining thermogenesis, as well as immune and neuroendocrine homeostasis in the face of feed restriction.

Beta Adrenergic Agonist Treatments. A cDNA microarray and 2-dimensional electrophoresis approach was used to study differential gene expression in pig adipose tissue following clenbuterol treatment (Zhang et al., 2007). Eighty-two EST were differentially expressed in microarray analyses and divided into 4 functional gene groups. Sixteen of the differentially expressed genes were related to cellular metabolism, including apolipoprotein (**APO**) -D and -R. Upregulation of APO-R expression at the RNA and protein levels indicated that it may be critical to clenbuterol-induced decrease in adipose tissue accretion (Zhang et al., 2007). The APO-R was also detected in adipose tissue from neonatal (Hausman et al., 2006) and growing pigs (Hausman et al., 2007). Furthermore, APO-R was among the most abundant genes expressed in a porcine adipose tissue full-length cDNA library (Chen et al., 2006). The discovery of the potential role of APO-R serves to illustrate the function and role of transcriptional profiling or gene microarray studies of adipose tissue since there is virtually no information on APO-R in any other species. Other work indicated that chronic feeding of the phenethanolamime ractopamine at 20 ppm decreased SREBP-1c, fatty acid synthase, and GLUT-4 expression in subcutaneous adipose tissue of finishing Pietran pigs (Halsey et al., 2003). Further, ractopamine also reduced mRNA abundance of adipose leptin, carnitine palmitoyl-carnitine transferase-1, fatty acid synthase, glucose transporter-4, and SREBP-1c in adipose tissue of finishing Duroc and Pietrain pigs (Reiter et al., 2007).

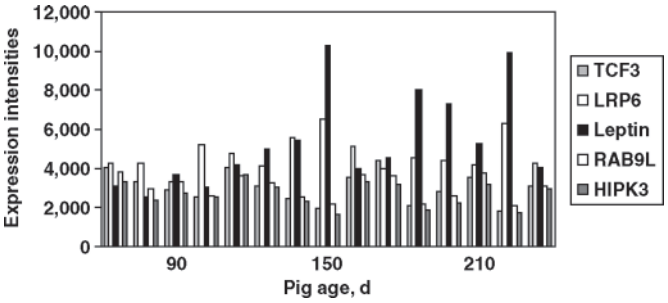

Figure 8. Middle subcutaneous adipose tissue microarray gene expression intensities for 5 individual pigs at each of the 3 ages studied (i.e., 90, 150, and 210 d) are shown. Significant simple linear regression ($P < 0.003$) coefficients were demonstrated between leptin gene expression patterns and expression patterns of 4 regulatory genes. Considering gene expression at the individual pig level, a positive association of TCF3 and LRP6 gene expression with leptin expression was demonstrated, whereas RAB9L and HIPK3 expression was negatively associated with leptin gene expression.

Quantitative Trait Loci for Fat Deposition and Composition

Fat deposition and composition phenotypes are typically quantitative traits in nature, which are usually controlled by multiple genes and environmental factors. During the past 15 yr, both genome scan and candidate gene approaches have been widely used to localize chromosome regions or functional genes that affect these

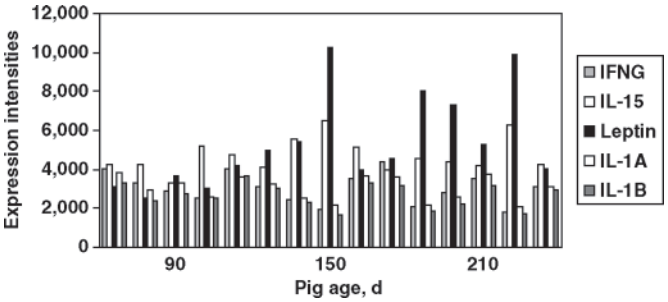

Figure 9. Middle subcutaneous adipose tissue gene expression intensities for 5 individual pigs at each of the 3 ages studied (i.e., 90, 150, and 210 d) are shown here. Significant simple linear regression ($P < 0.005$) coefficients were demonstrated between leptin gene expression patterns and expression patterns of 4 genes encoding secretory factors. When considering gene expression at the individual pig level, a positive association with leptin expression was noted only for IL-15 gene expression because IL-1A, IL-1B, and interferon-γ (IFNG) expression was negatively associated with leptin gene expression.

economically important traits (Jiang et al., 2007). It has been widely believed that the application of these genes/markers in livestock breeding programs will permit the development of new genetic technologies and open the way to realize the full genetic potential for improvement of meat production for maximum profits.

QTL and Candidate Genes for Fat Deposition and Composition in Swine. The current PigQTLdb (http://www.animalgenome.org/QTLdb/) has gathered a total of 1,831 QTL from 113 publications representing 316 different pig traits (Hu et al., 2007b; Rothschild et al., 2007). Among them, at least 520 significant or suggestive QTL were identified for 86 traits related to fat deposition and fatty acid composition in pigs. Figure 10 illustrates a total of 469 QTL central locations selected for 66 traits that are grouped into 14 clusters: abdominal fat (S1), backfat (average) thickness (S2), backfat at shoulder (S3), backfat at first rib (S4), backfat between 3rd and 4th rib (S5), backfat at 10th rib (S6), backfat at last rib (S7), backfat at last lumbar (S8), backfat weight (S9), fat percentage in carcass (S10), intermuscular fat percentage (S11), marbling (S12), fat androstenedione level (S13), and fatty acid composition (S14).

It should be noted that 469 QTL for fat deposition and composition are not evenly distributed in the porcine genome, ranging from 2 (on SSC16) to 68 (on SSC7). In particular, abundant fat-related QTL are identified on SSC1 (55), SSC2 (35), SSC4 (67), SSC6 (67), SSC7 (68), and X (42), respectively (Figure 10). Second, among these 14 clusters of traits, 8 are related to backfat measurements, but only the average backfat has been heavily investigated with the largest number of QTL identified in various reference populations (Hu et al., 2007b; Rothschild et al., 2007). Interestingly, QTL for the average backfat would overlap most of those for other backfat measurements. Third, although marbling and IMF content measure fat stored in muscle and they are well correlated ($r = 0.57$, $P < 0.0001$; Huff-Lonergan et al., 2002), their genetic backgrounds look quite different. For marbling in swine, QTL regions have been found on SSC1, SSC8, SSC10, SSC12, SSC14, and SSC17. However, for IMF content, QTL regions have been detected on SSC4, SSC7, and the porcine X chromosome, respectively. Only SSC6 harbors QTL regions for both marbling and IMF content (Figure 10).

Several candidate genes have also been identified to affect fat deposition in pigs. For example, distal-less homeobox 5 (Cheng et al., 2008), fatty acid binding protein 4 and 5 (Estelle et al., 2006), GH 1 and its releasing hormone (Franco et al., 2005), 11 β hydroxysteroid dehydrogenase isoform 1 (Otieno et al., 2005), IGF-1 (Estany et al., 2007), leptin receptor (Ovilo et al., 2005), malic enzyme 1 (Vidal et al., 2006), mitogen-activated protein kinase (MAPK) 8 (Otieno et al., 2005), PPARγ, coactivator-1α (Stachowiak et al., 2007), and pituitary specific transcription factor 1 (Franco et al., 2005) significantly influence backfat thickness in the carcass. Carbonic anhydrase 3 (Wang et al., 2006b) and fatty acid binding protein 3 (Arnyasi et al., 2006) were found to be associated with intramuscular fat content, whereas liver X receptor α (Yu et al., 2006), myosin light chain 2 fast skeletal (Wang et al., 2006a), and resistin (Otieno et al., 2005) significantly affect marbling in pork. Three genes, capping protein (actin filament) muscle Z-line, β (Yang et al., 2008), IGFBP2 (Wang et al., 2008b), and myosin light chain 2 fast skeletal (Wang et al., 2006b), have a significant impact on leaf fat weight. Nuclear receptor coactivators 1, 2, and 3 (Wang et al., 2008c) and SREB-1c (Chen et al., 2008) were found to have significant impact on IMF content. In addition, the PPARγC1A gene is also associated with abdominal fat in pigs (Stachowiak et al., 2007).

QTL and Candidate Genes for Fat Deposition and Composition in Cattle. The current Cattle Quantitative Trait Loci database (CattleQTLdb) has gathered 1,123 QTL from 71 publications published over more than 10 yr (Hu et al., 2007b). Interestingly, mapping QTL for fat deposition and composition has targeted quite a few phenotypes in both dairy and beef cattle. In dairy cattle, most work has focused on fat percentage (S1) and fat yield (S2) in milk, whereas in beef cattle, marbling (S3), and subcutaneous fat depth (S4) in carcass are 2 major targets related to adipogenesis (Figure 11).

A QTL mapping for milk fat percentage and fat yield indicated that both traits share some common genetic background. For example, chromosomes such as BTA6 and BTA14 with QTL rich for fat percentage also harbor abundant QTL for fat yield in milk (Figure 11). In contrast, candidate gene approach could not reveal many genes that are in common to control fat percentage/content and fat yield in milk. For example, αs1-casein, β-casein, and κ-casein genes (Velmala et al., 1995), defensin, β 4 (Wojdak-Maksymiec et al., 2006; Bagnicka et al., 2007), and signal transducer and activator of transcription 5A (Khatib et al., 2008) were reported to show effects on fat percentages or content in milk. Growth hormone (Yao et al., 1996; Grochowska et al., 2001) and its receptor (Aggrey et al., 1999), PPARγC1A (Weikard et al., 2005) and protease inhibitor (Khatib et al., 2005) were found to be associated with milk fat yield. Only 2 genes—osteopontin (Khatib et al., 2007) and oxidized LDL receptor 1 (Khatib et al., 2006)—affect both fat percentage and fat yield in milk.

Fortunately, QTL mapping for both marbling and subcutaneous fat depth in beef cattle revealed that they are unlikely to share the common genetic background (Figure 11), thus making it easier for the beef industry to select for marbling and against fat thickness. After reviewing QTL mapping for beef marbling in different populations, Jiang et al. (2007) observed that some QTL might be breed-specific (Jiang et al., 2007). For example, 7 bovine chromosomes, BTA2, BTA3, BTA16, BTA17, BTA23, BTA27, and BTA29, harbor QTL for marbling detected in American beef cattle breeds only.

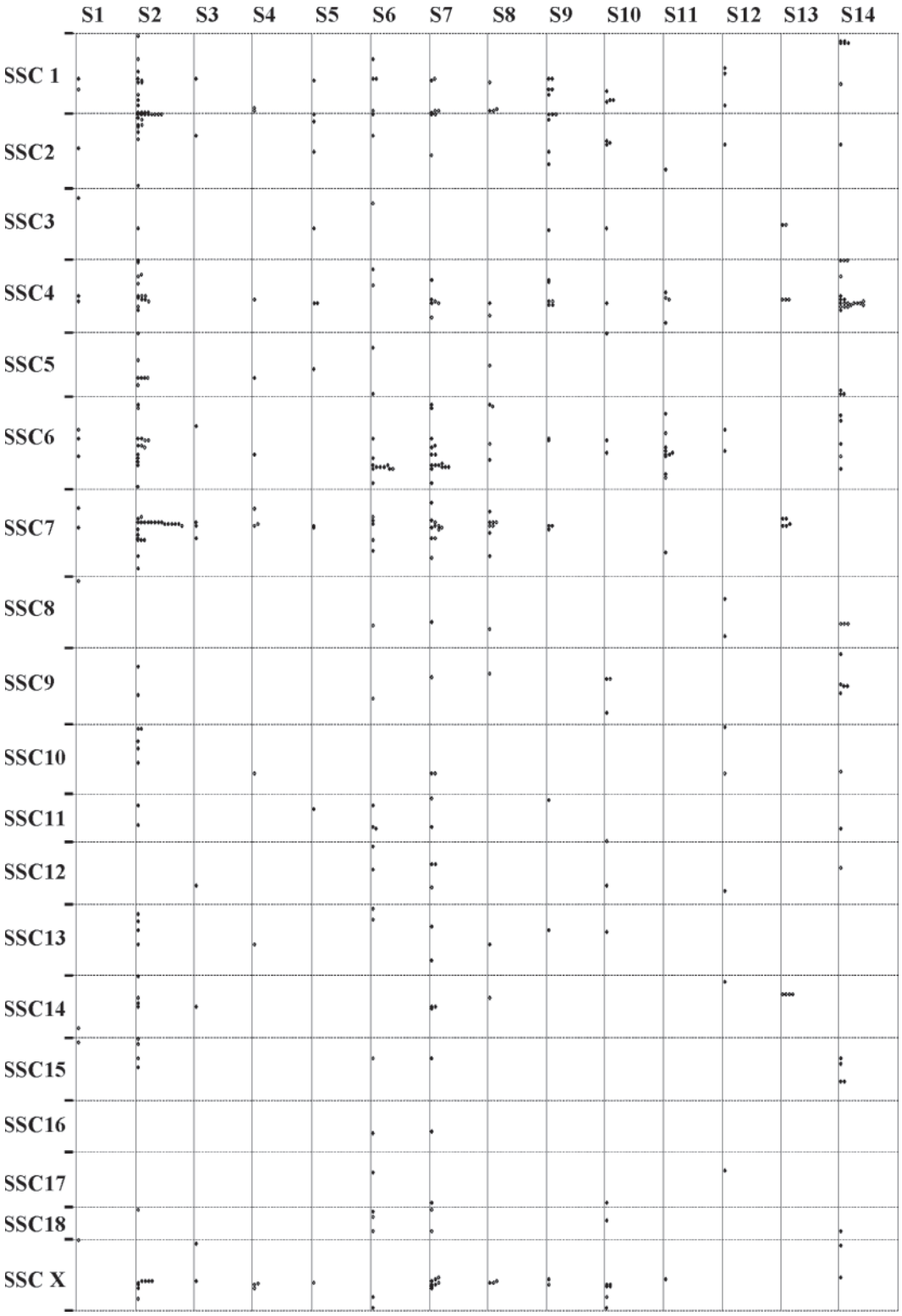

Figure 10. A total of 469 QTL central locations are selected for 66 traits of pigs that are grouped into 14 clusters: abdominal fat (S1), backfat (average) thickness (S2), backfat at shoulder (S3), backfat at first rib (S4), backfat between 3rd and 4th rib (S5), backfat at 10th rib (S6), backfat at last rib (S7), backfat at last lumbar (S8), backfat weight (S9), fat percentage in carcass (S10), intermuscular fat percentage (S11), marbling (S12), fat androstenone level (13), and fatty acid composition (S14).

However, 4 chromosomes, BTA4, BTA6, BTA7 and BTA13, are Asian-breed specific; they possess QTL for marbling found in Japanese Wagyu or Korean Hanwoo cattle only. The chromosomes BTA5, BTA8, BTA9, BTA10, and BTA14 have QTL regions in both breed sources, but the QTL center locations are not necessarily similar or close to each other. Several candidate genes have also been explored for their associations with both marbling and subcutaneous fat depth in beef cattle. For example, GH (Tatsuda et al., 2008), μ-calpain, (Cheong

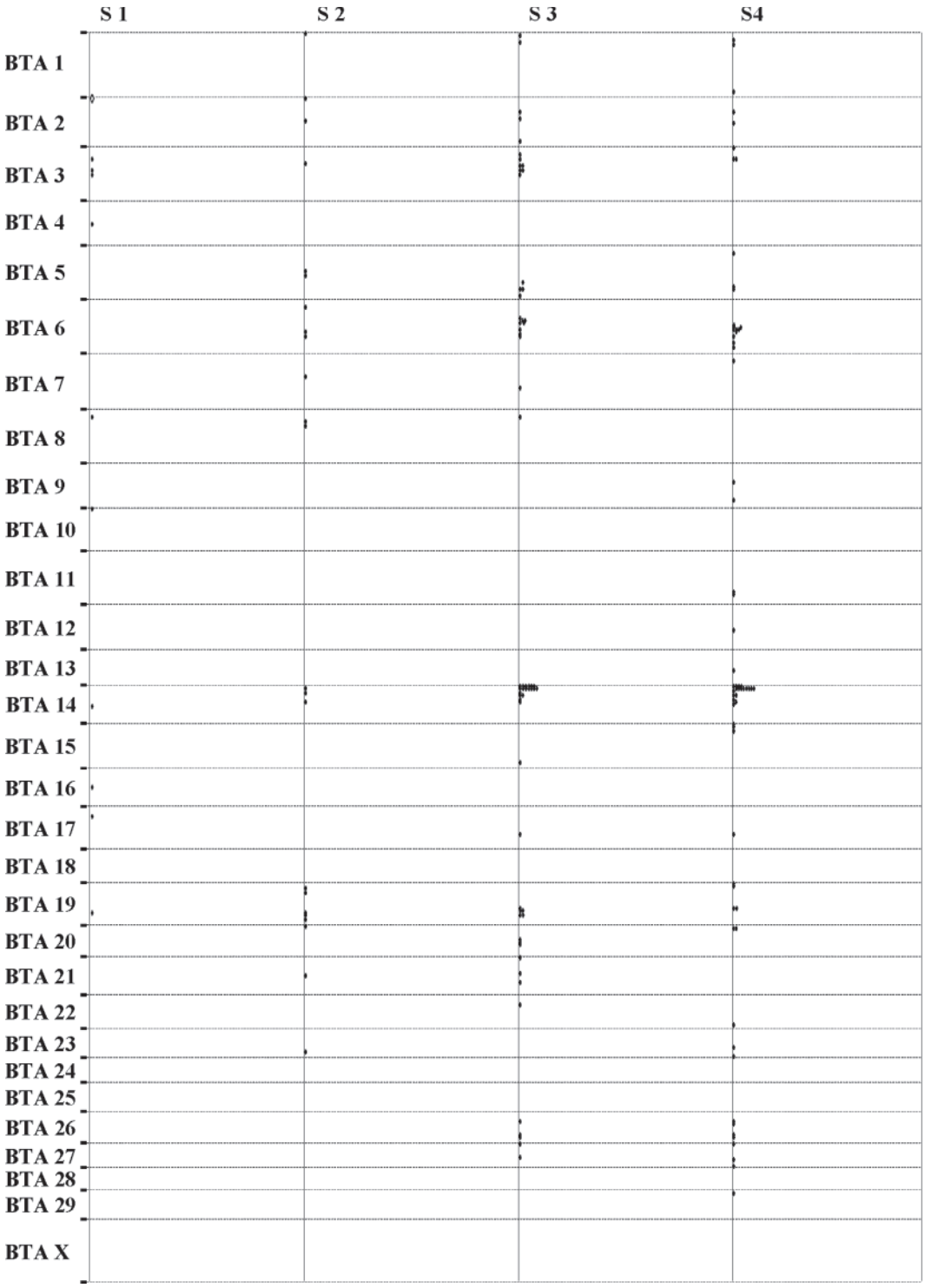

Figure 11. A total of 164 QTL central locations are selected for 4 traits of cattle: marbling score (S1), fat thickness (S2), fat percentage (S3), fat yield (S4).

et al., 2008), NPY (Sherman et al., 2008), and thyroglobulin (Wood et al., 2006) genes show significant effect on marbling, whereas FABP4 (Cho et al., 2008), IGF-2 (Sherman et al., 2008), and leptin (Buchanan et al., 2002; Schenkel et al., 2005) are associated with backfat thickness.

At the moment, information on QTL mapping for fatty acid composition seems very limited in both dairy and beef cattle. In dairy, there is one report on the FAS gene, which is associated with the fatty acid composition of milk fat (Morris et al., 2007). In beef, Taylor et al. (1998) reported a chromosome-wide scan of QTL for fatty acid composition on bovine chromosome 19 (Taylor et al., 1998). On the other hand, few candidate genes were also investigated for their associations with fatty acid composition in different beef breeds. For example, Raes et al. (2001) examined the intramuscular fatty acid composition in the 3 myostatin genotypes

(double-muscling, *mh/mh*; heterozygous, *mh/+*; normal, *+/+*) and found that the *mh/mh* animals had significantly greater P/S ratio and proportions of C20:5n-3 and C22:5n-3 relative to the sum of n-3 PUFA, but significantly less C18:3n-3 content and proportions of C20:4n-6 and C22:4n-6 relative to the sum of n-6 PUFA compared with the *+/+* animals (Raes et al., 2001). Taniguchi et al. (2004) identified a mis-sense mutation that causes an AA replacement from valine (type V) to alanine (type A) in the fifth exon of bovine stearoyl-CoA desaturase (**SCD1**) gene. The authors found that the SCD1 type A gene contributes to elevated MUFA percentage and lower melting point in intramuscular fat. Hoashi et al. (2007) found a large 84-bp insertion and a deletion in intron 5 of bovine SREBP-1 in Japanese Black cattle. Association analysis revealed that the deletion contributes to 1.3% elevated MUFA and 1.6°C lower melting point in intramuscular fat.

The Human Obesity Gene Map and Its Information Transfer to Livestock Species

To date, more than 300 genes and 400 QTL have been placed on the human obesity gene map (Rankinen et al., 2006). No doubt, the map provides us a unique reference to explore genes/QTL for fat deposition and composition in livestock species. In pigs, Kim et al. (2004) focused on 8 genes known to be associated with human obesity for their candidacy related to the pig growth and fat deposition QTL regions, including melanocortin receptors 3 and 4, agouti signaling protein and agouti-related protein, high-mobility group A family genes 1 and 2, PPARγ, and ghrelin (Kim et al., 2004). The authors found that associations between polymorphisms of these candidate genes and a variety of phenotypic measurements in pigs are in reasonable agreement with results from human and other animal studies. In beef cattle, workers have successfully tested 10 obesity-related genes, including corticotropin-releasing hormone (Wibowo et al., 2007), corticotropin-releasing hormone receptor 2 (Jiang et al., 2006), FABP4 (Michal et al., 2006), poly(A) polymerase associated domain containing 1 (Xiao et al., 2006), SCD1 (Jiang et al., 2008a), transcription factor A, mitochondrial (Jiang et al., 2005), urocortin 3 (Jiang et al., 2006), urotensin 2 (Jiang et al., 2008b), urotensin 2 receptor (Jiang et al., 2008b), and ubiquinol-cytochrome c reductase core protein I (Kunej et al., 2007). Therefore, cross-species candidate gene information transfer is a powerful means to determine the same causal genes that underlie the concordant QTL in both human and livestock species. Certainly, this comparative QTL mapping approach is worth further exploration because the same orthologous gene may have conserved functions in biological or biochemical pathways, and thus explain the same or similar variations of the concordant QTL among different species.

Conclusions

Advancements in meat animal production strategies, including genetic selection, nutrition, environmental strategies, etc., have successfully improved feed efficiency and growth rates of domestic meat animals over time. Reductions in total fat content of animal products have been achieved primarily by selection for leanness. Very little is known, however, about selective regulation of adipose deposition into desired depots, such as marbling in meat animals. As such, understanding the biology of preadipocytes and adipocytes is vital for altering meat animal carcass composition. Advances in research technologies, from stem cell and embryonic methods to molecular and genetic tools, now allow for investigation of the epigenetic processes and integrated regulatory networks that result in specific distribution of adipose tissues. Results from research using both contemporary tools and classic research methods, such as those described in this review, will enable a more complete understanding of adipose tissue biology that will be vital for improving meat animal carcass composition to meet the needs of producers and the expectations of consumers.

Future Directions

As consumers increase demand for healthy food options, the meat animal industry will focus more strongly on improved meat composition. In particular, altering the oleic acid, linolenic acid, n-3, or CLA content of animal products has been suggested as a means to create healthier animal products. Also, although no direct comparison has been made, empirical evidence suggests marbling content is less in current meat animals than those of several decades ago (Dunshea et al., 2005; Fortin et al., 2005). Current emphasis in selection programs for both cattle and pigs is on increasing intramuscular fat, without impacting subcutaneous fat. Every day, new scientific methods are developed that allow for targeted investigation of preadipocytes, adipocytes, adipose tissue, and interactions of adipose tissue and cells. In addition to cellular studies, a growing body of evidence suggests that the interaction of adipokines may impact the growth of skeletal muscle and that cytokines secreted from skeletal muscle may affect intramuscular adipocytes (Argiles et al., 2005; Nielsen and Pedersen, 2007), which has the potential to play a significant role in animal production. Emerging technologies such as protein array analysis, microRNA analysis, and transcriptome analysis will also be used to extend our knowledge beyond that obtained from classic techniques used to study the regulation of growth and development of adipose tissue and its various cell types. As our knowledge of basic adipose development and biology continues to grow, it is likely that we will refine control of adipose tissue and adipose effects on meat quality to an extraordinary degree. The potential

benefits to producers and consumers, as well as the biomedical field, will keep the biology and regulation of preadipocytes and adipocytes at the focus of scientific interest for many years to come.

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